Remarks

Claims 1-3 and 7-10 are pending. In view of the following remarks reconsideration and allowance of the claims is respectfully requested.

Restriction Requirement

Applicants acknowledge the maintenance of the Restriction Requirement. The present Office Action states that applicants' traversal was on the grounds that "the claimed inventions are not independent or distinct..." This statement is not correct. Applicants note for the record that at no place in applicants' traversal did applicants make this assertion.

Claim Rejections – 35 USC § 103

Claims 1-3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yein et al (US 5783407) in view of Falchuk (US 6902881), Lin et al (US 5284940) and DERWENT (AC No: 1987-173702). In this regard the Office Action further states the following:

> Claims are drawn to methods of determining/measuring biliverdin in a sample from avian or reptilian species comprising contacting the sample with biliverdin reductase, measuring change in absorbance at about 325 to about 750 nm and comparing with absorbance values from a control sample or a standard concentration curve.
>
> Yein et al teach a method of determining/measuring biliverdin (col. 2, lines 20-21) concentration in a sample comprising contacting the sample (col. 2, line 24, e.g. tissue) with an oxidizing enzyme (col. 2, lines 60-64), measuring a change in absorbance within a range of 325 to about 750 nm (col. 6, lines 15-21, lines 27-30, lines 51-53) and determining/measuring biliverdin concentration by comparing the absorbance values to a control or a standard curve (col. 7, lines 51-52 and lines 7.
>
> Falchuk teaches samples which comprise biliverdin, see col. 12, lines 36-41 and line 66. The sample is from an avian or reptilian species, note col. 27, line 4.
>
> Lin et al teach that biliverdin may be converted to bilirubin by the enzyme biliverdin reductase. Note col. 14, lines 58-60.
>
> DERWENT teaches that reductase enzyme is an oxidizing enzyme. See abstract, line 2.
>
> The claims differ from Yein et al in that a sample from an avian or reptile species, and biliverdin reductase is not disclosed.
>
> It would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to select a sample which comprises biliverdin from

snakes or birds and further to add the enzyme, bilverdin reductase, in an assay disclosed by Yein et al because biliverdin is clearly disclosed to be in snake and bird species by Falchuk and Lin et clearly teach bilverdin reductase and DERWENT teaches that reductases are oxidizing enzymes.

Thus, one of ordinary skill in the art would have expected successful results for determining biliverdin concentration in a bird or snake sample using an enzyme reaction mixture of the sample and biliverdin reductase since the enzyme is well recognized to be an oxidizing enzyme and can convert biliverdin to bilirubin and oxidizing enzymes can also convert bilirubin to biliverdin.

Hence, the determination/measurement of biliverdin would have been an expected successful result by such enzyme reaction mixture and to measure a change in absorbance between 325 to about 750 nm is clearly disclosed by Yein et al as noted above, or is at least suggested by Yein et al. Also, Yein et al clearly recognize that each of biliverdin and bilirubin can be determined or measured based on absorbance values taken and compared with absorbance values on a standard curve or from a control sample. The claimed process steps are well recognized by the cited prior art and one of skill would have been motivated to provide for these steps to determine and/or measure biliverdin concentration in a sample from an avian or reptilian species. The absorbance range is clearly suggested, if not taught, by the cited prior art and an increased biliverdin concentration in the sample is suggested. Since just as the enzyme reaction of bilirubin oxidase can be used to measure bilirubin by oxdizing bilirubin to biliverdin, the enzyme reaction of biliverdin reductase can be used to measure biliverdin by the conversion of biliverdin to bilirubin.

The claims are taught, or are at least suggested, and there is sufficient motivation demonstrated by the cited prior art to carry out the process steps as claimed to determine biliverdin concentration in a sample from birds or snakes. The claims are, therefore, rendered prima facie obvious over the cited prior art.

Yein et al. is directed to an assay used to detect in a test sample an analyte that undergoes auto-oxidation (col. 2, lines 7-8). More specifically, Yein et al. discloses the measurement of bilirubin. In contrast, biliverdin does not undergo auto-oxidation. This reference discloses biliverdin solely as the product of the oxidation reaction, and not as the object for detection. Yein et al. teaches a method of measuring bilirubin (i.e., the analyte) by contacting it with an oxidizing enzyme. The Yein et al. disclosure appears to be solely focused on a diagnostic assay for humans, as it mentions only patients, which applicants read as referring to humans. Column 2, lines 56-64 recite the following:

> The analyte can be selected from the group consisting of bilirubin, glucose, cholesterol, neutral fats, free fatty acids, phospholipids and uric *acids.* Preferably, the analyte is bilirubin.
>
> The enzyme can be selected from the group consisting of bilirubin oxidase, glucose oxidase, cholesterol oxidase, unease, acyl coenzyme A oxidase, choline oxidase, and glycerol-3-phosphate oxidase. Preferably, the analyte is bilirubin, and the product species is biliverdin.

In contrast, the present methods are directed to measuring biliverdin using a reducing enzyme. There is no mention in Yein et al. of a method of measuring biliverdin using a reducing enzyme. Yein et al. has no disclosure regarding any reducing enzyme, much less biliverdin reductase, which would not be functional in the method it discloses. When read in context, Yein et al. provides no information regarding a method of detecting biliverdin using a reducing enzyme. Furthermore, there is no motivation provided by this reference. Particularly, there is no mention of any animals other than humans. Thus, there is no suggestion to do anything that would be relevant to birds and reptiles, i.e., no suggestion to modify the disclosed method so it would work with birds or reptiles, which do not produce bilirubin. In fact, since bilirubin is not usually present in avian and reptile serum and urine, its measurement is not useful in evaluating liver disease or hemolytic disease in birds. Thus, this citation does not support a rejection of the claimed method.

Falchuk teach a method of stimulating differentiation of cells by contacting them with biliverdin. In the description of Figure 10, Falchuk states that "[t]he effects on proliferation by biliverdin purified from frog eggs are identical to those obtained with a commercial biliverdin preparation." Thus, Falchuk describes biliverdin from an amphibian source for the purpose of use in its differentiation experiments. This reference does not allude to the measurement of biliverdin and does not suggest any reason to measure biliverdin as an analyte in a bird or reptile. Also, there is no teaching of "samples which contain biliverdin" at

column 12, lines 36-41 and line 66 as stated in the Office Action. Additionally, contrary to the assertion in the Office Action, Falchuk do not teach that the biliverdin "sample is from an avian or reptilian species, note col. 27, line 4." Rather, it is the cells used in the differentiation experiments that are described as being from a bird or reptile. Column 27, lines 1-6 recites the following:

> Cells can be obtained from embryonic, post-natal, juvenile or adult neural tissue from any animal. By any animal is meant any multicellular animal which contains nervous tissue. More particularly, is meant any fish, reptile, bird, amphibian or mammal and the like. The most preferable donors are mammals, especially mice and humans.

As can be seen, there is no mention of biliverdin in the cited part of the Falchuk patent. This reference does not teach that biliverdin is present in snake and bird species. Thus, it does not provide the teaching missing from Yein et al., Lin et al. and the Derwent abstract. Even though it would not be sufficient by itself, the absence a teaching that biliverdin is present in birds and reptiles negates any motivation from this combination of art to detect biliverdin in birds and reptiles.

The Office Action cites a Derwent abstract as teaching "that reductase enzyme is an oxidizing enzyme." The abstract does refer in line 2 to the presence of "a oxidizing reductase." Initially, applicants question the translation, as it is not clear what is meant by "oxidizing reductase" as this term is found no-where in the PubMed database. Furthermore, even if such an enzyme exists, there is no basis, either in the abstract or any other place of record, which says that all reductases oxidize or, more relevantly, that biliverdin reductase oxidizes. In fact, biliverdin reductase is known as an oxidoreductases, because it reduces biliverdin to bilirubin and oxidizes NADPH (or NADH) to NADP+ (NAD+). It does not perform a dual oxidation and reduction of biliverdin; the enzyme heme oxygenase oxidizes

heme to biliverdin. The assertion that "biliverdin reductase ...is well recognized to be an oxidizing enzyme" is not relevant, because it does not oxidize bilirubin or biliverdin. Thus, it could not be routinely substituted in the method of Yein et al. to obtain any useful outcome, much less the claimed method. Furthermore, the fact that biliverdin is an oxidoreductase does not alter the fact that Yein et al. disclose a very different method than the method of the present claims.

Nothing in Yein et al. read in view of Falchuk, Lin et al. or the Derwent abstract suggests a reason to measure biliverdin as an endpoint, as none of them suggest an benefit of knowing how much biliverdin is present. In the absence of any teaching in the art of any reason to measure biliverdin as an endpoint, there is no basis to infer a general motivation to practice the claimed method, which measures biliverdin as an endpoint. Furthermore, there is nothing stated or implied in the cited combination that provides specific motivation to modifying the method of Yein et al. to detect biliverdin in birds and reptiles by adding biliverdin reductase to a sample containing biliverdin.

In summary, the combination of references does not teach every element of the claims, namely, the presence of biliverdin in birds and reptiles or the contacting of a bird or reptile sample with biliverdin reductase. The combination of references fails to provide any motivation to practice the claimed method. Thus, the combination does not support a prima facie case of obviousness. Withdrawal of this rejection and allowance of the claims is respectfully requested.

No fee is believed due; however, the Commissioner is hereby authorized to charge any additional fees that may be required or credit any overpayment to Deposit Account No. 14-0629.

Respectfully submitted,

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Gwendolyn D. Spratt — Date: 2-17-09